## REMARKS

Claims 1, 4-16, 18-24, and 29-31 are pending. Claims 30 and 31 are withdrawn from consideration. Claims 2, 3, 17, and 25-28 are cancelled without prejudice or disclaimer. Claim 18 is amended. Claim 32 is added. Accordingly, claims 1, 4-16, 18-24, and 29-32 are pending upon entry of the present amendment.

Support for claim 32, reciting "A therapeutic composition for the treatment or prophylaxis of multiple sclerosis, wherein the composition comprises a β-glucuronidase enzyme and myelin, the β-glucuronidase enzyme and the myelin being present in the composition at a dose which provides a beneficial effect to an individual in need of treatment." is found throughout the claims and specification as filed. Specifically, support for claim 32 is at least found at page 3, lines 2-3 of the filed specification. No new matter is added.

**Rejections under 35 U.S.C. § 112, first paragraph**

The Office Action at page 2 rejects claims 1-24 and 29 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. As claims 2, 3, and 17 are cancelled, the rejection is moot as to those claims. Regarding claims 1, 4-16, 18-24, and 29, the rejected claims are directed to compositions comprising β-glucuronidase enzyme and collagen or myelin for the treatment or prophylaxis of arthritis or multiple sclerosis, repectively, and kits comprising such compositions. Applicant respectfully disagrees with the enablement rejection and requests that it be withdrawn.

Throughout the present Office Action, the Examiner assert that the claims are directed to the treatment of **any** autoimmune condition. This is incorrect. Applicants note that in the Response dated January 5, 2009, the claims were amended to recite specifically arthritis and collagen. Therefore, the claims as currently amended are not directed to any autoimmune condition, but to arthritis and multiple sclerosis. Applicant respectfully requests the Examiner to note this amendment in determining the scope of the claims.

The standard set forth for enablement in 35 U.S.C. §112, first paragraph, requires that Applicant provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains ... to make and use" the invention. The proper test of enablement is set forth

in *United States v. Telectronics, Inc.*, (857 F.2d 778, 785, 8 USPQ2d at 1217, 1223 (Fed. Cir. 1988)):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

The examples provided in the specification clearly teach one of skill in the art how to make compositions containing β-glucuronidase enzyme and collagen for the treatment of arthritis. Specifically, Applicant describes a composition comprising the enzyme, β-glucuronidase, and the immunogen, type II collagen (page 9, 4th paragraph). Compositions containing the β-glucuronidase enzyme and collagen were injected into a widely accepted mouse model of rheumatoid arthritis, where the onset (e.g., at low dose) was delayed and the severity (e.g., at high dose) of arthritis was reduced based on results in a blinded study.

Specifically, Applicant states, "Animals were scored for clinical arthritis from day 17 to day 52 twice weekly by observation of joint redness and swelling. The study centre was blinded (page 9, 4th paragraph)." The features scored in the blinded study included joint swelling, redness, inflammation, and bone remodeling (page 11, 4th paragraph). In the low dose treatment group, a statistically significant difference in onset and arthritis severity was observed at day 29 (Figures 2 and 3, and page 12, second paragraph). Applicant discovered that the claimed composition "altered the course of arthritis in the experiment" by delaying arthritis progression (page 13, 1st paragraph). Significantly, this alteration in the progression of the disease occurred after a single treatment. Based on these results, it is likely that increased protection would be observed if further doses were given (page 13, 1st paragraph).

The severity of arthritis observed in mice that received a higher dose of the claimed composition was also significantly lessened. Applicant found that disease in the group that received the higher dose was much lower than expected, and was statistically significant (page 12, 4th paragraph). Regarding these results, Applicant states, "The alteration to the course of disease observed following high dose treatment is suggestive of a **potent anti-arthritic effect** (page 13, 4th paragraph; emphasis added)." In fact, following treatment with the claimed

compositions, Applicant found that levels of disease reduction were comparable to those observed when established anti-arthritic drugs were given (page 13, 4th paragraph).

The specification clearly contains a description of "how to make" the invention (e.g., page 3, line 9 - page 5, line 28 of the originally filed specification) and "how to use" the invention (e.g., page 2, line 31 – page 3, line 8; and page 5, line 29 – page 6, line 18 of the originally filed specification). Thus, the disclosures of the specification support the standard of enablement set forth in the first paragraph of 35 U.S.C. §112.

Applicant also submit herewith Appendix A disclosing supplemental data showing the effectiveness of the administration of β-glucuronidase enzyme and the immunogen myelin in treating an animal model of multiple sclerosis (i.e., Experimental Autoimmune Encephalomyelitis). As described in the Appendix, treatment with β-glucuronidase and myelin according to the compositions and methods of the invention was able to extend remission an extra three days, a 25% improvement over placebo at a single dose. Thus, Applicant provides another example of the use of β-glucuronidase enzyme and an immunogen to treat an autoimmune condition.

In support of the enablement rejection, the Examiner has cited two articles by Terr ("Unproven and Controversial Forms of Immunotherapy." Clinical Allergy and Immunology (2004) 18: 703-710 (hereinafter "Terr"), and "Unproven and Controversial Forms of Immunotherapy." Clinical Allergy and Immunology (1999) 12:479-488). Each of these articles provides a review of therapies that Terr considers unconventional or controversial. However, neither of these articles refutes the probative evidence provided by Applicant's disclosure and the disclosure submitted herewith in Appendix A. Moreover, the claims as currently amended recite the treatment of arthritis and multiple sclerosis.

Terr (2004) at page 707, third full paragraph states:

> Several published double-blind reports claim symptomatic improvements in adults or children with **allergic rhinitis or asthma** along with conflicting results of immunological changes [citations omitted].

Applicant respecfully submits that Terr's criticism of therapies involving the administration of β-glucuronidase are concluded solely based on the evaluation of studies

regarding treatment of **allergic rhinitis or asthma**. Terr is otherwise silent regarding the efficacy of any other therapies involving the administration of β-glucuronidase for the treatment of autoimmune conditions, e.g., arthritis and multiple sclerosis, as currently claimed. At page 707, second full paragraph, Terr states that proponents of therapies involving the administration of β-glucuronidase have claimed success in treating various additional autoimmune conditions including rheumatoid arthritis, but Terr cites no references or studies to back up his broader conclusion that **all** therapies involving the administration of β-glucuronidase for the treatment of autoimmune conditions are suspect. Thus, Terr's criticism of the therapies involving the administration of β-glucuronidase are anecdotal, at best. Rather Terr's conclusion represents a faulty generalization based on a subset of studies involving only two autoimmune conditions allergic rhinitis and asthma.

That is, Terr's prejudice against all therapies involving the administration of β-glucuronidase does not preclude that such therapies may work for other autoimmune conditions, e.g., as Applicant has shown for the treatment of arthritis and multiple sclerosis. With respect to the use of the enzyme, β-glucuronidase, in combination with any immunogen, Terr states that "**To date**, there have been no published research findings in patients treated by this method to substantiate this theory." [emphasis added]. Even if the effectiveness of previous studies involving treatment of allergic rhinitits and asthma have not been shown to Terr's satisfaction, Terr is careful to acknowledge that there are potentially other studies to be performed that could substantiate such therapies. Terr also states that "the presumed pharmacological property of β-glucuronidase on the immune system are based on anecdotal evidence only." Nevertheless, Terr's criticism that the therapy is unsupported by scientific evidence is overcome by the probative data disclosed in the specification and Appendix A submitted herewith. These disclosures by the Applicant would lead one of skill in the art to conclude that the claimed compositions are useful in treating or preventing autoimmune diseases, such as rheumatoid arthritis and multiple.

The claimed compositions are at least enabled by the examples present in the specification, which describe how to make and use a composition comprising an enzyme and an immunogen in *in vivo* experiments in an animal model of the autoimmune condition arthritis (pages 8-13). The Examiner questions the reliability of Applicant's data, stating that "the data

presented by the specification does not appear to be a reliable indicator that the skilled artisan could use to a predict successful therapeutic outcome for a patient group that is known to be extremely difficult to treat (Office action mailed October 15, 2007, page 5, 1st paragraph)." Applicant invites the Examiner's attention to *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), where the court states:

> [I]t is incumbent upon the Patent Office . . . to explain ***why*** it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is **inconsistent with the contested statement**. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. 439 F.2d at 224, 169 USPQ at 370 (Emphasis added).

In the present case, the Examiner apparently relies on Terr to provide the requisite evidence or reasoning to show that Applicant's invention lacks enablement; however, this reliance is misplaced. Terr provides no evidence or reasoning that is inconsistent with Applicant's disclosure. Terr stands for the principle that therapeutic methods must be based on objective scientific data. Applicant's disclosure of a blinded study showing treatment of an autoimmune disease with the claimed composition provides just such objective scientific data. Thus, Terr fails to support the lack of enablement rejection.

In support of the enablement rejection, the Examiner attempts to draw parallels between Terr's criticism of previous studies for the treatment of allergic rhinitis and asthma. The Office Action at page 5 states that "The data regarding groups B and C is not clear cut." Applicant respectfully disagrees. Applicant has presented a statistical analysis of the data at day 52 post induction in Figure 5, which indicates that group C and group B differ significantly. The likelihood that the two groups would differ in this way by random sorting is low, as shown in the calculated p value ($p<0.003$) (Figure 5). These results clearly indicate that group C, which received 50 ng/ml collagen and glucuronidase, showed a reduction in the severity of arthritis compared to group B, which received buffer control, and this effect can be statistically relied upon. Furthermore, Applicants respectfully disagree with the Examiner that "There is no substantial difference between the control group and those mice receiving the lower does [sic] (group A) [Office Action, page 5, 1st full paragraph)."

Contrary to the Examiner's assertion, Figure 2 shows a clear delay in onset of disease. Arthritis onset was delayed by about 7 days in group A mice, which received 50 fg/ml collagen and glucuronidase, compared to group B control mice (Figure 2). Additionally, in Figure 3, a marked reduction in disease severity was observed in mice treated with 50 fg/ml collagen and glucuronidase relative to control mice (page 10, fourth paragraph). A statistical comparison between groups A and B provided a calculated p value of <0.033 (Figure 3). A low p-value indicates that the likelihood is low that the observed effect is due to random sampling or is merely coincidental. It should be borne in mind that rheumatoid arthritis is a disease with a very slow and progressive onset and as such any delay in onset is a useful treatment of the disease. Based on these results, a person of skill in the art would reasonably conclude that the invention would be useful in treating or preventing autoimmune diseases.

The Office Action at page 5 states: "The calculated correlation factor is low and the data in Figure 3 and 5 shows a great deal of overlap of data points." Regarding the issue of the correlation factor, the measurement of p-value is different from that of the correlation factor [sic] or correlation coefficient. In statistics, correlation refers to the departure of **two** random variables from independence (i.e., curve fitting) and thus does not apply to either Figures 3 or 5 which do not depict such data. In most contexts, a correlation coefficient approaching 1 is desirable to show a correlation. However, regarding p-values, the lower the p-value the less likely the result is due to random sampling or is merely coincidental (i.e., the null hypothesis). A low p-value is desirable to show the significance of an observed effect, because it allows one a level of confidence to discount the null hypothesis. Regarding the statement that "the data in Figure 3 and 5 shows a great deal of overlap of data points," the power of statistical tools is to be able to analyze "noisy" data and evaluate whether the data are meaningful or significant. In this case, the low p-values indicate that the difference in the groups tested is significant.

The Examiner appears to question whether Applicant's results in an animal model of the autoimmune disease arthritis would be predictive of results in human therapy. Where Applicants disclose a working example, this fact weighs heavily in favor of enablement. M.P.E.P. §2164.02 states:

> An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention . . . the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

The Examiner has failed to show why Applicant's disclosed results in an animal model would fail to correlate with autoimmune disease.

M.P.E.P. §2164.02 is clear that "Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example." The Examiner has not provided any reason to doubt the mouse model of rheumatoid arthritis described by Applicant. Furthermore, M.P.E.P. §2164.02 elaborates that "a rigorous or an invariable exact correlation is not required," citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and **therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.** (Citations omitted.) [Emphasis added]

The Examiner has not provided a reason to doubt the mouse model of the autoimmune disease used to obtain the *in vivo* data disclosed in Applicant's specification.

The Office Action at page 6, has reinstated the rejection of claim 29, alleging that "the composition of claim 29 is not **the same composition** administered to the [rheumatoid arthritis] in the examples." [emphasis added] Applicant submits that it is known in the art how to calculate a Fishman unit of β-glucuronidase activity, which is the enzyme activity that increases the rate of release of phenolphthalein from phenolphthalein β-D-glucosiduronic acid at a temperature of 38° C by 1 μg. (see Wakabayashi and Fishman. J. Biol. Chem. 1961 236: 996-

1001). Moreover, the MPEP §2164.01 further points out that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Regardless, MPEP §2164.02 citing *In re Brana* is clear that the standard of enablement is one of reasonable correlation.:

> An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention.

Applicant submits that regardless of whether the dosages and amounts of the compounds in the composition being claimed are the same as those presented in the examples, the enablement requirement is satisfied as long as the claims reasonably correlate with the examples.

For the reasons detailed above, there is no reason why the compositions and methods being claimed would not be expected to work as described. Nor is undue experimentation required to practice the invention being claimed (e.g., the burden of determining the effectiveness of enzyme-potentiated desensitization (EPD), as alleged by the Office Action at page 6). Applicant has clearly satisfied the enablement requirement. Furthermore, Applicant presents data showing the treated of the autoimmune disease multiple sclerosis in an art-recognized animal model. In view of the above evidence and arguments, Applicants request that the enablement rejection be withdrawn.

## CONCLUSION

In view of the above amendment and response, respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the application with claims 1-24 and 29-31 presented herein. If a telephone call with Applicant's representative would be helpful in expediting prosecution of the application, Applicant invites the Examiner to contact the undersigned at the telephone number shown below.

Applicant believes that no additional fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 61190(50221).

Dated: October 28, 2009

Respectfully submitted,

Electronic signature: /Elbert Chiang, Ph.D./
Elbert Chiang, Ph.D.
Registration No.: 60,325
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5580
Attorneys/Agents For Applicant